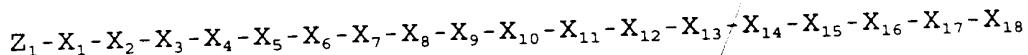


What Is Claimed Is:

1. An ApoA-I agonist comprising:  
(i) a 14 to 22-residue peptide or peptide analogue which  
5 forms an amphipathic  $\alpha$ -helix in the presence of lipids and  
which comprises the structural formula (I):



10  $X_1$  is Pro (P), Ala (A), Gly (G), Asn (N), Gln (Q) or D-Pro (p);

$X_2$  is an aliphatic amino acid;

$X_3$  is Leu (L);

$X_4$  is an acidic amino acid;

15  $X_5$  is Leu (L) or Phe (F);

$X_6$  is Leu (L) or Phe (F);

$X_7$  is a basic amino acid;

$X_8$  is an acidic amino acid;

$X_9$  is Leu (L) or Trp (W);

20  $X_{10}$  is Leu (L) or Trp (W);

$X_{11}$  is an acidic amino acid or Asn (N);

$X_{12}$  is an acidic amino acid;

$X_{13}$  is Leu (L), Trp (W) or Phe (F);

$X_{14}$  is a basic amino acid or Leu (L);

25  $X_{15}$  is Gln (Q) or Asn (N);

$X_{16}$  is a basic amino acid;

$X_{17}$  is Leu (L);

$X_{18}$  is a basic amino acid;

$Z_1$  is  $H_2N-$  or  $RC(O)NH-$ ;

30  $Z_2$  is  $-C(O)NRR$ ,  $-C(O)OR$  or  $-C(O)OH$  or a salt thereof;  
each R is independently -H, ( $C_1-C_6$ ) alkyl, ( $C_1-C_6$ ) alkenyl,  
( $C_1-C_6$ ) alkynyl, ( $C_5-C_{20}$ ) aryl, ( $C_6-C_{26}$ ) alkaryl, 5-20 membered  
heteroaryl or 6-26 membered alk heteroaryl or a 1 to 4-residue  
peptide or peptide analogue;

each " - " between residues  $X_n$  independently designates an amide linkage, a substituted amide linkage, an isostere of an amide or an amide mimetic; or

5 (ii) a deleted from of structural formula (I) in which at least one and up to eight of residues  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ ,  $X_5$ ,  $X_6$ ,  $X_7$ ,  $X_8$ ,  $X_9$ ,  $X_{10}$ ,  $X_{11}$ ,  $X_{12}$ ,  $X_{13}$ ,  $X_{14}$ ,  $X_{15}$ ,  $X_{16}$ ,  $X_{17}$  and  $X_{18}$  are deleted; or

10 (iii) an altered form of structural formula (I) in which at least one of residues  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ ,  $X_5$ ,  $X_6$ ,  $X_7$ ,  $X_8$ ,  $X_9$ ,  $X_{10}$ ,  $X_{11}$ ,  $X_{12}$ ,  $X_{13}$ ,  $X_{14}$ ,  $X_{15}$ ,  $X_{16}$ ,  $X_{17}$  or  $X_{18}$  is conservatively substituted with another residue.

15 2. The ApoA-I agonist of Claim 1 which exhibits at least about 38% LCAT-activation activity as compared with human ApoA-I.

20 3. The ApoA-I agonist of Claim 1 which is the altered form of structural formula (I).

4. The ApoA-I agonist of Claim 3 in which the hydrophobic residues are fixed according to structural formula (I) and at least one non-fixed residue is conservatively substituted with another residue.

25 5. The ApoA-I agonist of Claim 4 in which:

$X_1$  is Pro (P), D-Pro (p), Gly (G), Asn (N) or Ala

(A);

$X_2$  is Ala (A), Leu (L) or Val (V);

30  $X_3$  is Leu (L);

$X_5$  is Leu (L) or Phe (F);

$X_6$  is Leu (L) or Phe (F);

$X_7$  is Leu (L) or Trp (W);

$X_{10}$  is Leu (L) or Trp (W);

35  $X_{13}$  is Leu (L), Trp (W) or Phe (F);

$X_{17}$  is Leu (L); and

at least one of  $X_4$ ,  $X_7$ ,  $X_8$ ,  $X_{11}$ ,  $X_{12}$ ,  $X_{14}$ ,  $X_{15}$ ,  $X_{16}$  and  $X_{18}$  is conservatively substituted with another residue.

5       6. The ApoA-I agonist of Claim 3 in which the hydrophilic residues are fixed according to structural formula (I) and at least one non-fixed residue is conservatively substituted with another residue.

10      7. The ApoA-I agonist of Claim 6 in which:

$X_4$  is Asp (D) or Glu (E);  
 $X_7$  is Arg (R), Lys (K) or Orn;  
 $X_8$  is Asp (D) or Glu (E);  
 $X_{11}$  is Asn (N) or Glu (E);  
 $X_{12}$  is Glu (E);  
 $X_{14}$  is Lys (K), Arg (R) or Orn;  
 $X_{15}$  is Gln (Q) or Asn (N);  
 $X_{16}$  is Lys (K), Arg (R) or Orn;  
 $X_{18}$  is Asn (N) or Gln (Q); and

15      20     at least one of  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_5$ ,  $X_6$ ,  $X_9$ ,  $X_{10}$ ,  $X_{13}$  and  $X_{17}$  is conservatively substituted with another residue.

25      8. The ApoA-I agonist of Claim 6 in which  $X_3$  is Leu (L),  $X_6$  is Phe (F),  $X_9$  is Leu (L) or Trp (W),  $X_{10}$  is Leu (L) or Trp (W) and at least one of  $X_1$ ,  $X_2$ ,  $X_5$ ,  $X_{13}$  and  $X_{17}$  is conservatively substituted with another residue.

30      9. The ApoA-I agonist of Claim 5 or 7 in which the substituting residue is classified within the same sub-category as the substituted residue.

35      10. The ApoA-I agonist of Claim 1 which is the deleted form of structural formula (I).

11. The ApoA-I agonist of Claim 10 in which one helical turn of the peptide or peptide analogue is deleted.

12. The ApoA-I agonist of Claim 1 which is an 18-residue peptide or peptide analogue of structural formula (I).

13. The ApoA-I agonist of Claim 12 in which:

5 the "-" between residues designates -C(O)NH- ;  
Z<sub>1</sub> is H<sub>2</sub>N- ; and  
Z<sub>2</sub> is -C(O)OH or a salt thereof.

14. The ApoA-I agonist of Claim 13, in which:

10 X<sub>1</sub> is Pro (P), Ala (A), Gly (G), Asn (N) or D-Pro  
(p) ;

X<sub>2</sub> is Ala (A), Val (V) or Leu (L) ;

X<sub>3</sub> is Leu (L) ;

X<sub>4</sub> is Asp (D) or Glu (E) ;

X<sub>5</sub> is Leu (L) or Phe (F) ;

X<sub>6</sub> is Leu (L) or Phe (F) ;

X<sub>7</sub> is Arg (R), Lys (K) or Orn ;

X<sub>8</sub> is Asp (D) or Glu (E) ;

X<sub>9</sub> is Leu (L) or Trp (W) ;

20 X<sub>10</sub> is Leu (L) or Trp (W) ;

X<sub>11</sub> is Glu (E) or Asn (N) ;

X<sub>12</sub> is Glu (E) ;

X<sub>13</sub> is Leu (L), Trp (W) or Phe (F) ;

X<sub>14</sub> is Arg (R), Lys (K) or Orn ;

25 X<sub>15</sub> is Gln (Q) or Asn (N) ;

X<sub>16</sub> is Arg (R), Lys (K) or Orn ;

X<sub>17</sub> is Leu (L) ; and

X<sub>18</sub> is Arg (R), Lys (K) or Orn .

30 15. The ApoA-I agonist of Claim 1 which is selected from the group consisting of:

peptide 191 PVLDLLRELLEELKQQLK\* (SEQ ID NO:191) ;

peptide 192 PVLDLFLKELLEELKQQLK\* (SEQ ID NO:192) ;

peptide 193 PVLDLFLRELLEELKQQLK\* (SEQ ID NO:193) ;

35 peptide 194 PVLELFRELLEELKQQLK\* (SEQ ID NO:194) ;

peptide 195 PVLELFKELLEELKQQLK\* (SEQ ID NO:195);  
peptide 196 PVLDLFRELLEELKNKLK\* (SEQ ID NO:196);  
peptide 197 PLLDLFRELLEELKQQLK\* (SEQ ID NO:197);  
peptide 198 GVLDLFRELLEELKQQLK\* (SEQ ID NO:198);  
5 peptide 199 PVLDLFRELWEELKQQLK\* (SEQ ID NO:199);  
peptide 200 NVLDLFRELLEELKQQLK\* (SEQ ID NO:200);  
peptide 201 PLLDLFKELLEELKQQLK\* (SEQ ID NO:201);  
peptide 202 PALELFKDLLEELRQKLR\* (SEQ ID NO:202);  
10 peptide 203 AVLDLFRELLEELKQQLK\* (SEQ ID NO:203);  
peptide 204 PVLDFFRELLEELKQQLK\* (SEQ ID NO:204);  
peptide 205 PVLDLFREWLEELKQQLK\* (SEQ ID NO:205);  
peptide 206 PLLELLKELLEELKQQLK\* (SEQ ID NO:206);  
peptide 207 PVLELLKELLEELKQQLK\* (SEQ ID NO:207);  
15 peptide 208 PALELFKDLLEELRQRLK\* (SEQ ID NO:208);  
peptide 209 PVLDLFRELLNELLQQLK (SEQ ID NO:209);  
peptide 210 PVLDLFRELLEELKQQLK (SEQ ID NO:210);  
peptide 211 PVLDLFRELLEELQOLO\* (SEQ ID NO:211);  
peptide 212 PVLDLFOELLEELQOOLK\* (SEQ ID NO:212);  
peptide 213 PALELFKDLLEEFRQRLK\* (SEQ ID NO:213);  
20 peptide 214 PVLDLFRELLEELKQQLK\* (SEQ ID NO:214);  
peptide 215 PVLDLFRELLEEWKQQLK\* (SEQ ID NO:215);  
peptide 229 PVLELFERLLEDLQKKLK (SEQ ID NO:229);  
peptide 230 PVLDLFRELLEKLEQQLK (SEQ ID NO:230);  
peptide 231 PLLELFKELLEELKQQLK\* (SEQ ID NO:231);  
25

in either the N- and/or C-terminal blocked or unblocked forms.

16. A multimeric ApoA-I agonist which exhibits at least about 38% LCAT activation activity as compared with human ApoA-I and which has the structural formula (II):

(II)

HH{LL<sub>m</sub>-HH}<sub>n</sub>LL<sub>m</sub>-HH

or a pharmaceutically acceptable salt thereof, wherein:

each  $m$  is independently an integer from 0 to 1;

$n$  is an integer from 0 to 10;

each "HH" is independently a peptide or peptide

5 analogue according to Claim 1;

each "LL" is independently a bifunctional linker;

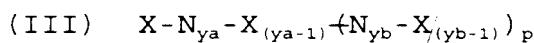
and

each " - " independently designates a covalent  
linkage.

10

17. A multimeric ApoA-I agonist which exhibits at least  
about 38% LCAT activation activity as compared with human  
ApoA-I and which has the structural formula (III):

15



*Sub B2*  
or a pharmaceutically acceptable salt thereof, wherein:

each  $X$  is independently  $HH-(LL_m-HH)_n-LL_m-HH$ ;

each  $HH$  is independently a core peptide of structure  
(I) or an analogue or mutated, truncated, internally deleted  
or extended form thereof as described herein;

each  $LL$  is independently a bifunctional linker;

each  $m$  is independently an integer from 0 to 1;

each  $n$  is independently an integer from 0 to 8;

25

$N_{y_a}$  and  $N_{y_b}$  are each independently a multifunctional  
linking moiety where  $y_a$  and  $y_b$  represent the number of  
functional groups on  $N_{y_a}$  and  $N_{y_b}$ , respectively;

each  $y_a$  or  $y_b$  is independently an integer from 3 to

8;

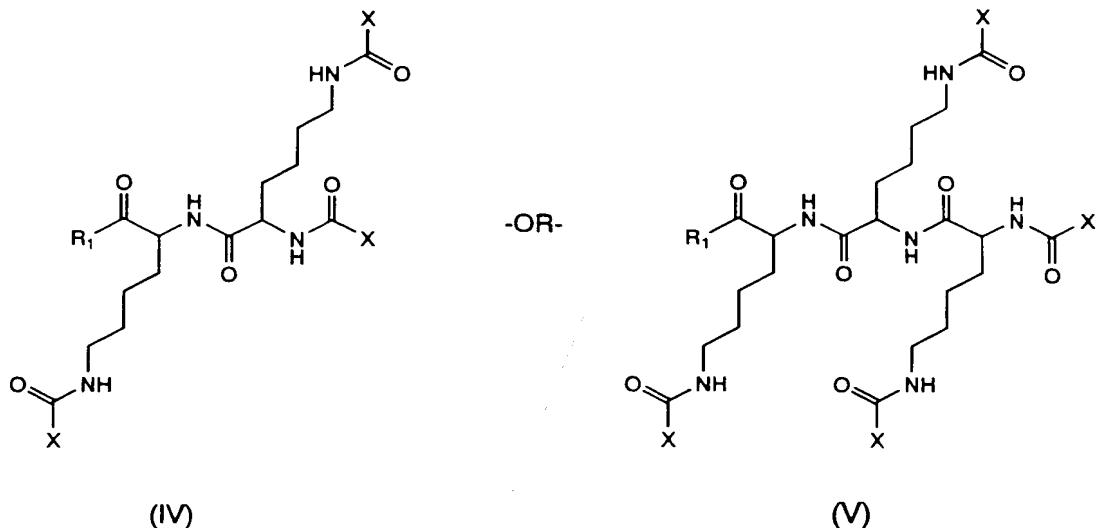
30

$p$  is an integer from 0 to 7; and

each " - " independently designates a covalent bond.

35

18. A multimeric ApoA-I agonist which exhibits at least  
about 38% LCAT activation activity as compared with human  
ApoA-I and which has the structural formula (IV) or (V):



or a pharmaceutically acceptable salt thereof, wherein:

each  $X$  is independently  $HH(LL_m-HH)_nLL_m-HH$ ;

each HH is independently a peptide or peptide analogue according to Claim 1;

each LL is independently a bifunctional linker;

each  $n$  is independently an integer from 0 to 1;

each  $m$  is independently an integer from 0 to 8;

R<sub>1</sub> is -OR or -NRR; and

each R is independently -H, (C<sub>1</sub>-C<sub>6</sub>) alkyl, (C<sub>1</sub>-C<sub>6</sub>) alkenyl, (C<sub>1</sub>-C<sub>6</sub>) alkynyl; (C<sub>5</sub>-C<sub>20</sub>) aryl (C<sub>6</sub>-C<sub>26</sub>) alkaryl, 5-20 membered heteroaryl or 6-26 membered alk(hetero)aryl.

15. 19. The multimeric ApoA-I agonist of Claim 16, 17 or 18  
in which the bifunctional linker is cleavable.

20. The ApoA-I multimeric agonist of Claim 16, 17 or 18 in which n is 0.

21. The multimeric ApoA-I agonist of Claim 20 in which m is 0.

5 22. The multimeric ApoA-I agonist of Claim 16, 17 or 18 in which each HH is independently a peptide according to Claim 13.

10 23. The multimeric ApoA-I agonist of Claim 16, 17 or 18 in which each HH is independently a peptide according to Claim 14.

15 24. The multimeric ApoA-I agonist of Claim 16, 17 or 18 in which each HH is independently a peptide according to Claim 15.

20 25. An ApoA-I agonist-lipid complex comprising an ApoA-I agonist and a lipid, wherein the ApoA-I agonist is a peptide or peptide analogue according to Claim 1, a multimeric ApoA-I agonist according to Claim 16, a multimeric ApoA-I agonist according to Claim 17, or a multimeric ApoA-I agonist according to Claim 18.

25 26. The ApoA-I agonist-lipid complex of Claim 25 in which the ApoA-I agonist is a peptide according to Claim 12.

27. The ApoA-I agonist-lipid complex of Claim 25 in which the ApoA-I agonist is a peptide according to Claim 13.

30 28. The ApoA-I agonist-lipid complex of Claim 25 in which the ApoA-I agonist is a peptide according to Claim 14.

29. The ApoA-I agonist-lipid complex of Claim 25 in which the ApoA-I agonist is a peptide according to Claim 15.

35 30. The ApoA-I agonist-lipid complex of Claim 25 in which the lipid is sphingomyelin.

31. The ApoA-I agonist-lipid complex of Claim 25 which is in the form of a lyophilized powder.

32. The ApoA-I agonist-lipid complex of Claim 25 which  
5 is in the form of a solution.

33. A pharmaceutical composition comprising an ApoA-I agonist and a pharmaceutically acceptable carrier, excipient or diluent, wherein the ApoA-I agonist is a peptide or peptide analogue according to Claim 1, a multimeric ApoA-I agonist according to Claim 16, a multimeric ApoA-I agonist according to Claim 17, or a multimeric ApoA-I agonist according to Claim 18.

15 34. The pharmaceutical composition of Claim 33 in which the ApoA-I agonist is a peptide according to Claim 12.

35. The pharmaceutical composition of Claim 33 in which the ApoA-I agonist is a peptide according to Claim 13.

20 36. The pharmaceutical composition of Claim 33 in which the ApoA-I agonist is a peptide according to Claim 14.

37. The pharmaceutical composition of Claim 33 in which  
25 the ApoA-I agonist is a peptide according to Claim 15.

30 38. The pharmaceutical composition of Claim 33, 34, 35, 36 or 37, in which the ApoA-I agonist is in the form of an ApoA-I agonist-lipid complex, said complex comprising the ApoA-I agonist and a lipid.

35 39. The pharmaceutical composition of Claim 38 in which the ApoA-I agonist-lipid complex is in the form of a lyophilized powder.

40. A method of treating a subject suffering from a disorder associated with dyslipidemia, said method comprising the step of administering to the subject an effective amount of the ApoA-I agonist of Claim 1.

5

41. The method of Claim 40 in which the ApoA-I agonist is in the form of a pharmaceutical composition, said composition comprising the ApoA-I agonist and a pharmaceutically acceptable carrier, excipient or diluent.

10

42. The method of Claim 40 in which the ApoA-I agonist is in the form of an ApoA-I agonist-lipid complex, said complex comprising the ApoA-I agonist and a lipid.

15

43. The method of Claim 40 in which the disorder associated with dyslipidemia is hypercholesterolemia.

44. The method of Claim 40 in which the disorder associated with dyslipidemia is cardiovascular disease.

20

45. The method of Claim 40 in which the disorder associated with dyslipidemia is atherosclerosis.

25

46. The method of Claim 40 in which the disorder associated with dyslipidemia is restenosis.

47. The method of Claim 40, in which the disorder associated with dyslipidemia is HDL or ApoA-I deficiency.

30

48. The method of Claim 40, in which the disorder associated with dyslipidemia is hypertriglyceridemia.

49. The method of Claim 40, in which the disorder associated with dyslipidemia is metabolic syndrome.

35

50. A method of treating a subject suffering from septic shock, said method comprising the step of administering to the subject an effective amount of the ApoA-I agonist of Claim 1.

5 51. The method of Claim 40 or 50 in which said subject  
is a human.

10 52. The method of Claim 40 or 50 in which about 0.5 mg/kg to about 100 mg/kg ApoA-I agonist is administered to said subject.